

**REMARKS**

Entry of the foregoing, reexamination, and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

**Summary**

As is correctly reflected in the Office Action Summary, Claims 91-117 are pending. Claims 99-112 were withdrawn as purportedly corresponding to non-elected subject matter. Claims 91-98 and 113-117 were rejected for the reasons discussed below. No acknowledgment has been made to a claim for domestic priority and such acknowledgment is respectfully sought.

**Amendments**

By the foregoing amendments, Claims 91-98 and 113-117 were canceled without prejudice or disclaimer. Applicants reserve the right to file one or more continuation and/or divisional applications directed to the previously-presented subject matter.

Also by the foregoing amendments, new Claims 118-130 were added. These claims correspond to former Claims 91-98 and 113-117, but have been redrafted to more accurately define Applicants' invention. Support for new Claims 118-130 may be found throughout the Specification. No new matter has been added.

Finally by the foregoing amendments, Claims 99-100, 102-103, 105-108, and 110-112 were amended to correct dependency, in light of the cancellation of Claims 91-98. These amendments were minor and clerical in nature. No new matter was added.

**Improper Markush Rejection**

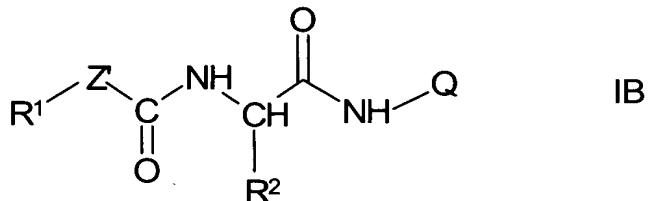
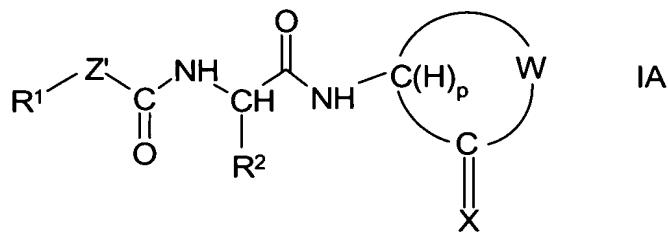
Turning now to the Official Action, Claims 91-98 and 113-117 were rejected as purportedly drawn to an improper Markush group. *See Office Action, Page 2.* According to the Examiner, Claims 91-98 and 113-117 lack unity of invention. *Id.* Specifically, the Examiner maintains that the "variables R<sup>1</sup> and the ring formed by W, together with -C(H)<sub>p</sub>C(=X), and Q are defined in such a way that they keep changing the core of the compound that determines the classification." *Id.* This rejection is respectfully traversed.

Whether a Markush grouping is proper is decided on a case-by-case basis. *In re Harnisch*, 631 F.2d 716, 722 (C.C.P.A. 1980); *In re Jones*, 74 U.S.P.Q. 149, 151 (C.C.P.A. 1947). A Markush grouping is proper where the substances grouped have a community of chemical and physical characteristics which justify their inclusion in a common group, and such inclusion is not repugnant to the principles of scientific classification. *In re Schechter*, 205 F.2d 185, 189 (C.C.P.A. 1953).

In determining the propriety of a Markush grouping, compounds are to be considered as a whole, and should not be broken down into elements or other compounds. *Jones*, 74 U.S.P.Q. at 151. Moreover, any differences among members of the group must be weighed against similarities. *Id.*

**1. The Compounds Must Be Considered As A Whole**

In the instant case, there are two formulae, IA and IB,<sup>1</sup> which figure predominantly in the Markush rejection:



In rejecting the Claims as purportedly drawn to an improper Markush group, the Examiner states, "[t]he ring formed by W, together with -C(H)<sub>p</sub>C(=X), and Q are defined in such a way that they keep changing the core of the compound that determines the classification."

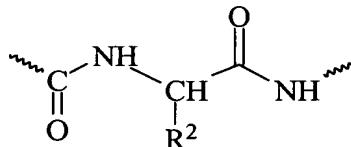
*See Official Action, Page 2.* The Examiner's position does not consider the N-acetyl substituted amino acid amides *as a whole*, but instead immediately focuses on the terminal portion of each formula. The Examiner's emphasis on this portion, and not the whole compound, runs contrary to a proper Markush analysis. *See Jones, 74 U.S.P.Q. at 151.*

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<sup>1</sup> For further discussion below, these compounds are referred to as "N-acetyl substituted amino acid amides," wherein "N-acetyl" refers to the R<sup>1</sup>-Z'-C(O)- group; "amino acid amide" refers to the -NH-(CH-R<sup>2</sup>)C(O)-NH- group; and "substituted" refers to either the cyclic structure or "Q" in formulae IA and IB, respectively.

**2. The Compounds Possess A Community Of Chemical And Physical Characteristics Which Justify Their Inclusion In A Common Group**

"From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. The graphic formulae ... are mere symbols by which compounds can be identified, classified, and compared. But a formula is not a compound and while it may serve in a claim to *identify* what is being patented ... the *thing* that is patented is not the formula but the compound identified by it." *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963). The N-acetyl substituted amino acid amides identified by graphic formulae IA and IB share a community of chemical characteristics, including the fact that these compounds inhibit  $\beta$ -amyloid peptide release and/or synthesis. Therefore, these compounds are useful in the prevention of Alzheimer's Disease. *See Specification, Page 8, Line 25 to Page 12, Line 19*. In addition, these compounds share a common structural element in that they all contain a common N-acetyl amino acid amide group of the formula:



When assayed for  $\beta$ -amyloid peptide production inhibition activity in cells using the assay described in Example Bio-1, it was shown that the compounds of formulae IA and IB provided significant inhibition of  $\beta$ -amyloid peptide production, as compared to the control. *See Specification, Pages 735-736*. Over 800 compounds of formulae IA and IB were prepared and assayed.<sup>2</sup> The identity of each of these compounds is listed in: Table C-1 (Compounds 8C 1-511, Pages 418-535 of the Specification); Table C-3 (Compounds 8C 512-601, Pages 539-554 of the Specification); Table C-4 (Compounds 7C 1-220, Pages

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<sup>2</sup> For the purpose of this discussion, isolated isomers of R and S were considered as additional compounds.

558-598 of the Specification, including replacement Page 597, filed July 26, 2001); and Table C-5 (Compounds 7C 221-244, Pages 602-606 of the Specification).

In view of the above, it is evident that the common N-acetyl amino acid amide group, together with the cyclic structure of formula IA or Q of formula IB, provide for a class of compounds possessing  $\beta$ -amyloid inhibition properties. Such compounds can include those having ring structures as set forth in the Tables spanning Pages 105-150 of the Specification. All of these compounds share the ability to inhibit  $\beta$ -amyloid peptide synthesis. Accordingly, their inclusion in a common group is justified, and such inclusion is not repugnant to the principles of scientific classification. *See Schechter*, 205 F.2d at 189.

### **3. Summary**

Based on the foregoing, it is evident that when the N-acetyl substituted amino acid amides of Formula IA and Formula IB are considered as a whole, they have a community of chemical and physical characteristics which justify their inclusion in a common group, and such inclusion is not repugnant to the principles of scientific classification. Accordingly, Applicants respectfully request withdrawal of the improper Markush group rejection against Claims 91-95, 104, 109-122, 131, and 136-145.

### **Rejection Under 35 U.S.C. § 112, Second Paragraph**

Claim 94 was rejected under 35 U.S.C. § 112, Second Paragraph, as purportedly indefinite. This rejection is respectfully traversed.

Not to acquiesce in the Examiner's rejection, but solely to facilitate prosecution, Claim 94 has been canceled. Accordingly, this rejection has been rendered moot.

### **Rejection Under 35 U.S.C. § 112, First Paragraph**

Claims 92, 96, 98, and 113-117 were rejected under 35 U.S.C. § 112, First Paragraph, as being purportedly not enabled for preventing the onset of AD in humans. This rejection is respectfully traversed.

To expedite prosecution, and not to acquiesce in the Examiner's rejection, Claims 92, 96, 98, and 113-117 have been canceled. Accordingly, this rejection has been rendered moot. New Claims 118-130 pertain to methods for inhibiting  $\beta$ -amyloid peptide synthesis and/or release, and thus do not raise the enablement query.

**CONCLUSION**

In summary, Applicants maintain that the outstanding rejections have been either obviated or rendered moot. From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions relating to this Response, or the application in general, it would be greatly appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,  
BURNS, DOANE, SWECKER & MATHIS, L.L.P.

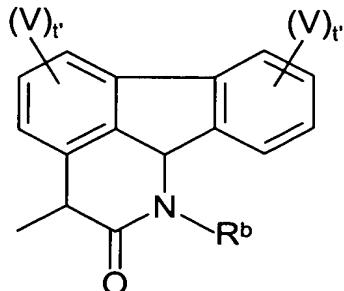
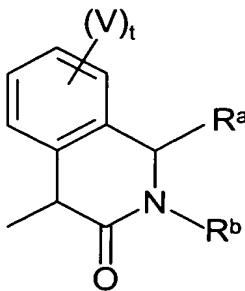
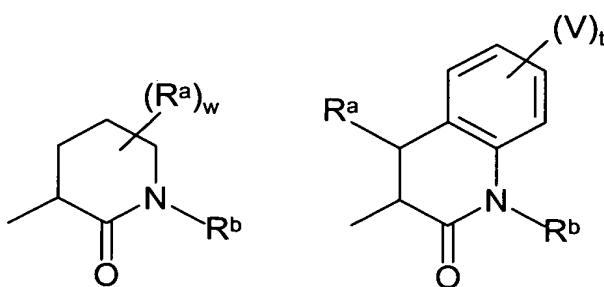
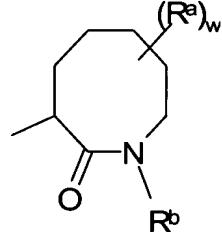
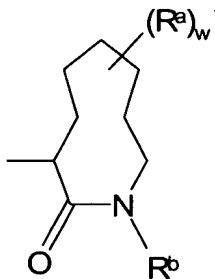
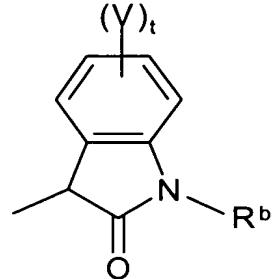
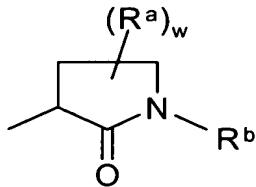
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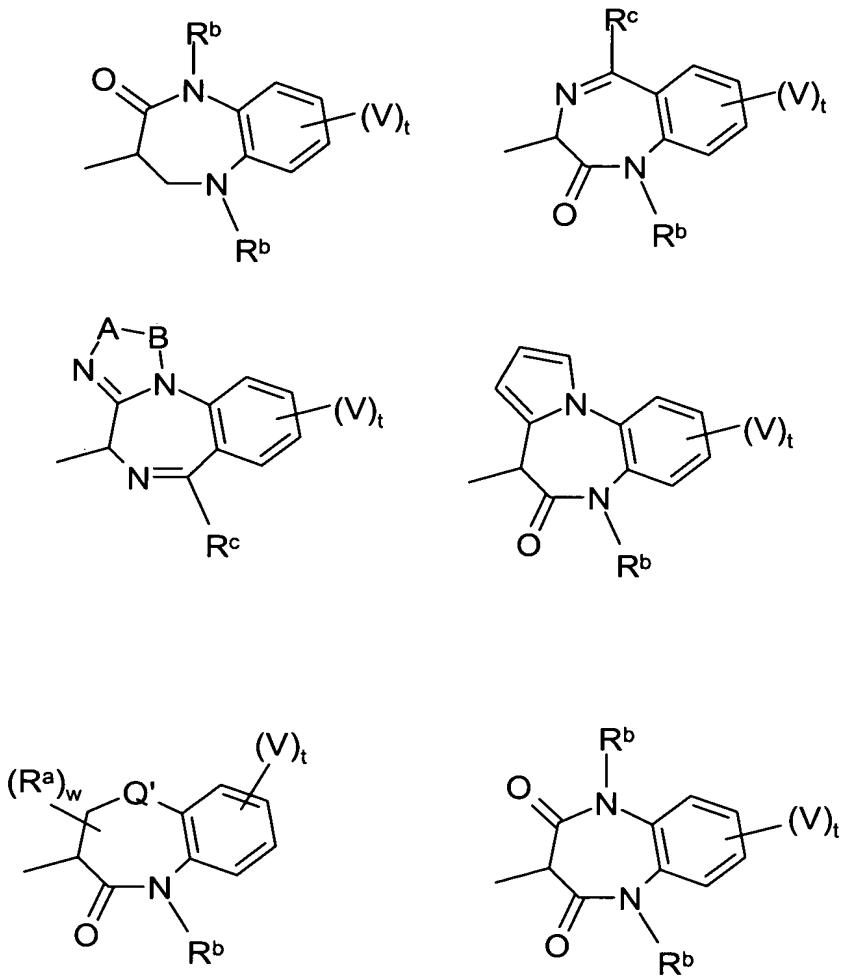
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**Marked-up Claims 99-100, 102-103, 105-108, and 110-112**

99. (Once Amended) The method according to Claim 122, 123, or 124, [Claims 95, 96 or 97] wherein Q is selected from the group having the formula:



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**Marked-up Claims 99-100, 102-103, 105-108, and 110-112**

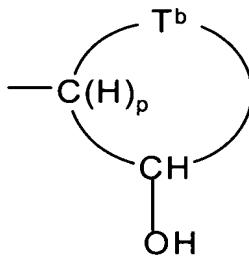


wherein A-B is selected from the group consisting of alkylene, alkenylene, substituted alkylene, substituted alkenylene and -N=CH-; Q' is oxygen or sulfur; each V is independently selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, optionally substituted alkaryl, optionally substituted

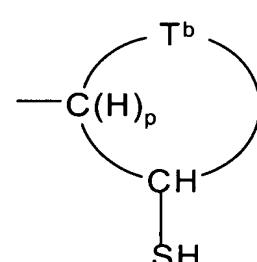
**Attachment to Amendment and Reply Dated December 10, 2002**  
**Marked-up Claims 99-100, 102-103, 105-108, and 110-112**

aryl, optionally substituted aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, optionally substituted heteroaryl, thioalkoxy, substituted thioalkoxy and trihalomethyl;  $R^a$  is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, carboxyl, carboxyl alkyl, cyano and halo;  $R^b$  is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic;  $R^c$  is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, cycloalkyl, and substituted cycloalkyl;  $t$  is an integer from 0 to 4;  $t'$  is an integer from 0 to 3; and  $w$  is an integer from 0 to 3.

100. (Once Amended) The method according to Claim 122, 123, or 124, [Claims 95, 96 or 97] wherein Q is a monocyclic or fused polycyclic ring having the formula:



$\sigma$



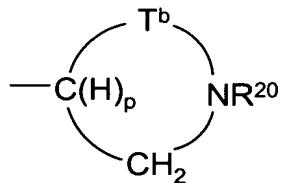
wherein  $p$  is an integer equal to 0 or 1 such that when  $p$  is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when  $p$  is one, the ring is saturated at the carbon atom of ring attachment to NH;

$T^b$  is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene,  $-(R^{21}Z^a)_qR^{21}-$  and  $-Z^aR^{21}-$  where  $Z^a$  is a substituent

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selected from the group consisting of -O-, -S- and >NR<sup>20</sup>, each R<sup>20</sup> is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R<sup>21</sup> is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z<sup>a</sup> is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and q is an integer of from 1 to 3.

102. (Once Amended) The method according to Claim 122, 123, or 124, [Claims 95, 96 or 97] wherein Q is a group having the formula:



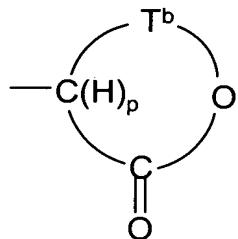
wherein p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

T<sup>b</sup> is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, -(R<sup>21</sup>Z<sup>a</sup>)<sub>q</sub>R<sup>21</sup>- and -Z<sup>a</sup>R<sup>21</sup>- where Z<sup>a</sup> is a substituent selected from the group consisting of -O-, -S- and >NR<sup>20</sup>, each R<sup>20</sup> is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R<sup>21</sup> is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the

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proviso that when  $Z^a$  is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and  $q$  is an integer of from 1 to 3.

103. (Once Amended) The method according to Claim 122, 123, or 124, [Claims 95, 96 or 97] wherein Q is a group having the formula:

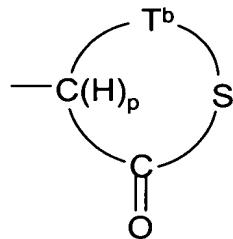


wherein  $p$  is an integer equal to 0 or 1 such that when  $p$  is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when  $p$  is one, the ring is saturated at the carbon atom of ring attachment to NH;

$T^b$  is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene,  $-(R^{21}Z^a)_qR^{21-}$  and  $-Z^aR^{21-}$  where  $Z^a$  is a substituent selected from the group consisting of -O-, -S- and  $>NR^{20}$ , each  $R^{20}$  is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each  $R^{21}$  is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when  $Z^a$  is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and  $q$  is an integer of from 1 to 3.

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105. (Once Amended) The method according to Claim 122, 123, or 124, [Claims 95, 96 or 97] wherein Q is selected from the group having the formula:

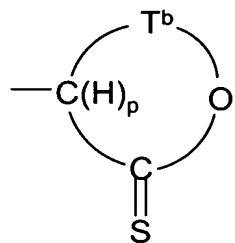


wherein  $p$  is an integer equal to 0 or 1 such that when  $p$  is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when  $p$  is one, the ring is saturated at the carbon atom of ring attachment to NH;

$T^b$  is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene,  $-(R^{21}Z^a)_qR^{21-}$  and  $-Z^aR^{21-}$  where  $Z^a$  is a substituent selected from the group consisting of  $-O-$ ,  $-S-$  and  $>NR^{20}$ , each  $R^{20}$  is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each  $R^{21}$  is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when  $Z^a$  is  $-O-$  or  $-S-$ , any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the  $-O-$  or  $-S-$ , and  $q$  is an integer of from 1 to 3.

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**Marked-up Claims 99-100, 102-103, 105-108, and 110-112**

106. (Once Amended) The method according to Claim 122, 123, or 124, [Claims 95, 96 or 97] wherein Q has the formula:

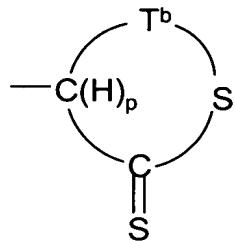


wherein  $p$  is an integer equal to 0 or 1 such that when  $p$  is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when  $p$  is one, the ring is saturated at the carbon atom of ring attachment to NH;

$T^b$  is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene,  $-(R^{21}Z^a)_qR^{21-}$  and  $-Z^aR^{21-}$  where  $Z^a$  is a substituent selected from the group consisting of  $-O-$ ,  $-S-$  and  $>NR^{20}$ , each  $R^{20}$  is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each  $R^{21}$  is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when  $Z^a$  is  $-O-$  or  $-S-$ , any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the  $-O-$  or  $-S-$ , and  $q$  is an integer of from 1 to 3.

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**Marked-up Claims 99-100, 102-103, 105-108, and 110-112**

107. (Once Amended) The method according to Claim 122, 123, or 124, [Claims 95, 96 or 97] wherein Q has the formula:

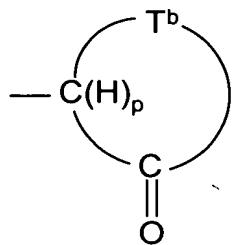


wherein  $p$  is an integer equal to 0 or 1 such that when  $p$  is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when  $p$  is one, the ring is saturated at the carbon atom of ring attachment to NH;

$T^b$  is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene,  $-(R^{21}Z^a)_qR^{21}-$  and  $-Z^aR^{21}-$  where  $Z^a$  is a substituent selected from the group consisting of  $-O-$ ,  $-S-$  and  $>NR^{20}$ , each  $R^{20}$  is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each  $R^{21}$  is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when  $Z^a$  is  $-O-$  or  $-S-$ , any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the  $-O-$  or  $-S-$ , and  $q$  is an integer of from 1 to 3.

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**Marked-up Claims 99-100, 102-103, 105-108, and 110-112**

108. (Once Amended) The method according to Claim 122, 123, or 124, [Claims 95, 96 or 97] wherein Q has the formula:

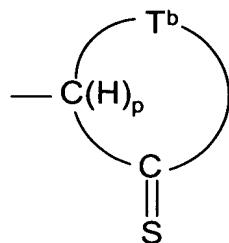


wherein  $p$  is an integer equal to 0 or 1 such that when  $p$  is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when  $p$  is one, the ring is saturated at the carbon atom of ring attachment to NH;

$T^b$  is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene,  $-(R^{21}Z^a)_qR^{21-}$  and  $-Z^aR^{21-}$  where  $Z^a$  is a substituent selected from the group consisting of  $-O-$ ,  $-S-$  and  $>NR^{20}$ , each  $R^{20}$  is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each  $R^{21}$  is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when  $Z^a$  is  $-O-$  or  $-S-$ , any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the  $-O-$  or  $-S-$ , and  $q$  is an integer of from 1 to 3.

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**Marked-up Claims 99-100, 102-103, 105-108, and 110-112**

110. (Once Amended) The method according to Claim 122, 123, or 124, [Claims 95, 96 or 97] wherein Q has the formula:

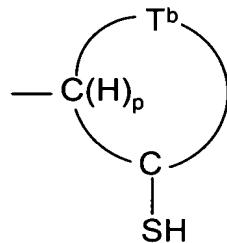


wherein *p* is an integer equal to 0 or 1 such that when *p* is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when *p* is one, the ring is saturated at the carbon atom of ring attachment to NH;

T<sup>b</sup> is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, -(R<sup>21</sup>Z<sup>a</sup>)<sub>q</sub>R<sup>21</sup>- and -Z<sup>a</sup>R<sup>21</sup>- where Z<sup>a</sup> is a substituent selected from the group consisting of -O-, -S- and >NR<sup>20</sup>, each R<sup>20</sup> is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R<sup>21</sup> is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z<sup>a</sup> is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and *q* is an integer of from 1 to 3.

**Attachment to Amendment and Reply Dated December 10, 2002**  
**Marked-up Claims 99-100, 102-103, 105-108, and 110-112**

111. (Once Amended) The method according to Claim 122, 123, or 124, [Claims 95, 96 or 97] wherein Q has the formula:

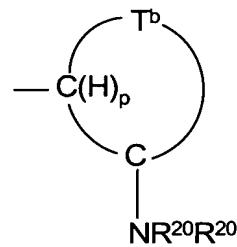


wherein *p* is an integer equal to 0 or 1 such that when *p* is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when *p* is one, the ring is saturated at the carbon atom of ring attachment to NH;

*T<sup>b</sup>* is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, -(R<sup>21</sup>Z<sup>a</sup>)<sub>q</sub>R<sup>21</sup>- and -Z<sup>a</sup>R<sup>21</sup>- where Z<sup>a</sup> is a substituent selected from the group consisting of -O-, -S- and >NR<sup>20</sup>, each R<sup>20</sup> is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R<sup>21</sup> is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z<sup>a</sup> is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and *q* is an integer of from 1 to 3.

**Attachment to Amendment and Reply Dated December 10, 2002**  
**Marked-up Claims 99-100, 102-103, 105-108, and 110-112**

112. (Once Amended) The method according to Claim 122, 123, or 124, [Claims 95, 96 or 97] wherein Q has the formula:



wherein  $p$  is an integer equal to 0 or 1 such that when  $p$  is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when  $p$  is one, the ring is saturated at the carbon atom of ring attachment to NH;

$T^b$  is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene,  $-(R^{21}Z^a)_qR^{21}-$  and  $-Z^aR^{21}-$  where  $Z^a$  is a substituent selected from the group consisting of  $-O-$ ,  $-S-$  and  $>NR^{20}$ , each  $R^{20}$  is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each  $R^{21}$  is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when  $Z^a$  is  $-O-$  or  $-S-$ , any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the  $-O-$  or  $-S-$ , and  $q$  is an integer of from 1 to 3.